Amendments to the Specification:

1. On page 10, replace the description of Figure 3 with the following:

--Figure 3. Distribution of unselected nucleotide substitutions along the Ramos V_H (SEQ ID NO: 15; SEQ ID NO: 128 – nucleic acid and amino acid sequences, respectively).--

2. On page 10, replace the description of Figure 6 with the following:

--Figure 6. Sequence table summarizing mutations in V_H other than single nucleotide substitutions. The mutations are:

A62 GGTCCT^{TCAGTGG}TTACTA (SEQ ID NO: 16)

A120 GTGGAT^{T}GGGGAA (SEQ ID NO: 17)

A276 TATTAC$^{TGTG.18bp.TACT}$AGGGCG (SEQ ID NO: 18)

A306 GAGGTA^{C}GGTATG (SEQ ID NO: 19)

B93 CCGCCA^{G}CCCCA (SEQ ID NO: 20)

B98 AGCCC^{C}AGGGAA (SEQ ID NO: 21)

B227 TGAGCT^{CTGTC}AACGCC (SEQ ID NO: 22)

C82 TGGAGT$^{TGGA.37bp.GAGT}$GGATTG (SEQ ID NO: 23)

C209 AGCACC^{TCTTCCCTGAAGTT}GAGCTC (SEQ ID NO: 24)

C187 ATATCA^{GTACACACGTCCAAGA}AGCACC (SEQ ID NO: 25)

U26 CGGAGA^{CC}CTGCC (SEQ ID NO: 26)

U199 ACGTCC^{AAG}AAGCAC (SEQ ID NO: 27)

U208 AAGCAG^{C}TTTCTC (SEQ ID NO: 28)

U268 GCGAGA^{GTTATTA}CTAGGG (SEQ ID NO: 29)

A255 ^{TGTGCGAGAGTTATTA}CGAGAGTTATTA^{CTAGGG} (SEQ ID NO: 30)

A113 $^{GGCTGGAGTGGATTGGG.62bp.TATC}$AGTGGATTGGG.62bp.TATC^{AGTAGA} (SEQ ID NO: 31)

U43 ^{ACCTGCGGTGTTTAT}GGTGTTTAT^{GGTGGG} (SEQ ID NO: 32)

U318 ^{GGACGTCTGGGGCCA}ACGTCTGGGGCCA^{AGGGAC} (SEQ ID NO: 33)

D27 GGAGAC^{CCTCA}CCTGCG (SEQ ID NO: 34)

D31 ACCCTC^{A}CCTGCG (SEQ ID NO: 35)

D219 CCTGAA^{G}TTGAGC (SEQ ID NO: 36)

D150 CACCAA^{C}TACAAC (SEQ ID NO: 37)

D109 AAGGGG^{C}TGGAGT (SEQ ID NO: 38)

E28 CCCTCA^{CCTGC}GGTGTT (SEQ ID NO: 39)

E81 CTGGAG$^{TTGGA..37bp..TGGAG}$TGGATT (SEQ ID NO: 40)

E88 TGGATC^{CGCC}AGCCCC (SEQ ID NO: 41)

E92 CGCCA^{G}CCCCCA (SEQ ID NO: 42)

E136 AATCAT^{AGTGGAAGCACCAACTA}CAACCC (SEQ ID NO: 43)

F66 CTTCAC^{TGGTTACTACT}GGAGTT (SEQ ID NO: 44)

F183 TATCAT^{ATCAGTA}ACACGT (SEQ ID NO: 45)

F215 TCTCCC$^{TGAA.18bp.CGCC}$GCGGAC (SEQ ID NO: 46)

F267 TGCGAG^{AG}TTATTA (SEQ ID NO: 47)

D55 $^{TATGGTGG.41bp.AGGG}$GTGG.41bp.AGGG^{AAGG} (SEQ ID NO: 48)

D123 ^{GATTGGGGAAATCAATCATAGTGGAAGC}GGAAATCAATCATAGGGAAGC^{ACCAAC} (SEQ ID NO: 49)

F85 $^{AGTTGGAT.10bp.CCCA}$GGAT.10bp.CCCA^{GGGA} (SEQ ID NO: 50)

D3 GGTCGC$^{AGGACTGT}_{GACCC}$TGAAGC (SEQ ID NO: 51)

D56 $^{ATGGTGGG.50bp.CAGGG}$GGTGGG.50bp.CAGGG^{AAGGGG} (SEQ ID NO: 52)

D71 GTGGTT$^{A}_{GGG}$CTACTG (SEQ ID NO: 53)

D75 TTACTA$^{C}_{GG}$TGGAGTT (SEQ ID NO: 54)

D126 TGGGA$^{AATCAATCAT}_{GGG}$AGTGGA (SEQ ID NO: 55)

D223 AAGTTG $^{AG}_{GACCCGGC}$ CTCTGTG (SEQ ID NO: 56)

D232 ^{TCTGTGAACGCCGC}GCCCCCGTCCTGTGAACGCCGC^{GGACAC} (SEQ ID NO: 57)

D235 ^{GTAAAC}GGAGG^{GCCGCG} (SEQ ID NO: 58)

D252 GGCTGT$^{GTATTACTGT}_{TCC}$GCGAGA (SEQ ID NO: 59)

D268 GCGAGA$^{GT}_{AGG}$TATTATT (SEQ ID NO: 60)

D275 TTATTA $^{C}_{GG}$TAGGGC (SEQ ID NO: 61)

D332 AAGGGA$^{C}_{AG}$CAC (SEQ ID NO: 62)

E3 GGGCGC$^{AGGA.51bp.CTTC}_{GT}$AGTGGT (SEQ ID NO: 63)

E51 TGTTTA$^{TGGT.15bp.TACT}_{AGACC}$ACTGGAG (SEQ ID NO: 64)

E80 ACTGGA$^{G}_{CCC}$TTGGAT (SEQ ID NO: 65)

E263 ACTGTG$^{CGAGAGTTATTACT}_{GGTG}$AGGGCG (SEQ ID NO: 66)

F89 GGATCC$^{GCCAGCCCCAGGG}_{AGG}$AAGGGG (SEQ ID NO: 67)

F168 CCTCAA$^{AGAGTCGAGT}_{GGG}$CACCAT (SEQ ID NO: 68)

F195 AGACAC$^{GTCCAAGAAG}_{AGGGC}$CACCTC (SEQ ID NO: 69)

F199 ACGTCC$^{AAGAAG}_{CT}$ACCCTGA (SEQ ID NO: 70)

F242 CCGCGG$^{ACACGGCTGTGTATTACTGT}_{GGA}$GCGAGA (SEQ ID NO: 71)

F260 ATTACT$^{GTG}_{CGTGA}$CGAGAG (SEQ ID NO: 72)

F264 CTGTGC$^{GAGAG.46bp.CGTC}_{ACA}$TGGGGC (SEQ ID NO: 73)

B123 GATTGG$^{G}_{A}$AAATC (SEQ ID NO: 74)

C109 AAGGGT^{C}TGGAGT (SEQ ID NO: 75)

A16 ^{TTGAAGCCTTCGGACT}GAAGCCTTCGGAGA^{CCCTGT} (SEQ ID NO: 76)

U180 ^{AGTCACCATATCAA}ACCATATCAG^{TAGACA} (SEQ ID NO: 77)

D45 CTGCGCG^{GTTTATGGTGGGT}CCTTCA (SEQ ID NO: 78)

D164 CGTCCCC^{CAAG}AGTCGA (SEQ ID NO: 79)

D216 CTCCCTT$^{AAG.22bp.CGGA}$CACGGC (SEQ ID NO: 80)

E11 GACTGT^{T}AAAGCC (SEQ ID NO: 81)

E54 TTATGGA$^{GGG.25bp.GTTG}$GATCCG (SEQ ID NO: 82)

F188 TATCAGG^{AGACACGTCCAGAA}GCACCT (SEQ ID NO: 83)

F220 CTGAAGC^{TGAGCTCTGTG}AACGCC (SEQ ID NO: 84).--

3. On page 10, please replace the description of Figure 7 with the following:

--Figure 7. Comparison of sequences isolated from VH genes of Ramos cells which have lost anti-idiotype (anti-Id1) binding specificity. Nucleotide substitutions which differ from the starting population consensus are shown in bold. Predicted amino acid changes

are indicated, also in bold type. The nucleotide sequence and amino acid sequence of the VH Ramos gene depicted is SEQ ID NO: 15 and SEQ ID NO: 128.--

4. On page 11, please replace the description of Figure 11 with the following:

--Figure 11. V_H sequence (SEQ ID NO: 15; SEQ ID NO: 128) derived from streptavidin-binding Ramos cells. Figure 11 CONT'D shows the VL sequence of SEQ ID NO: 85' SEQ ID NO: 129. Nucleotide changes observed in comparison with the V_H sequence of the starting population, and predicted amino acid changes, are shown in bold.--

5. On page 11, please replace the description of Figure 16 with the following:

--Figure 16. V_H (SEQ ID NO: 15; SEQ ID NO: 128) and V_L (SEQ ID NO: 85; SEQ ID NO: 129) sequences of round 6 selected IgM.--

6. On page 12, please replace the description of Figure 12 with the following:

--Figure 21. Analysis of Ig sequences of unsorted DT40 populations after one month of clonal expansion. The sequence of Figure 21 d is SEQ ID NO: 86.--

7. On page 12, please replace the description of Figure 23 with the following:

--Figure 23. A dynasty of IgMs from DT40 specific for a rat immunoglobulin idiotype. Cells were subjected to six rounds of selection using an aggregate of biotinylated-rat S7 IgG2a, monoclonal antibody (Ab)/FITC-streptavidin to yield DT-Ab3, which was then subjected to a further three rounds of sorting with a direct PE-Ab conjugate to yield DTAb6. (a) Analysis of the binding of biotinylated Ab/FITC-Strep aggregate as well as ofPE-Ab to DT-Ab3 and DT-Ab6 cells. (b) Binding of IgM in the supernatant of DTAb3, 5 and 6 cells to the S7 Ab monitored by ELISA using plates coated with S7 Ab and detection with anti-chicken IgM. Supernatants were controlled for total IgM titres. No binding by the DT-Ab6 IgM was detected to a wide variety of rat hybridoma and chimaericmAbs of different isotypes (generously provided by G. Butcher and MBruggemann (not shown)).(c) Binding of DT-Ab6 IgM to S7 rat IgG Ab coated on to the plate is competed by S7 Ab itself but scarcely by normal rat serum. The S7 (stock at

0.5 mg/ml) and rat serum competitors were used at the dilutions indicated. (d) DT-Ab6 IgM can be used to stain S7 hybridoma cells. Staining was detected by flow cytometry of fixed, permeabilised cells, detecting using FITC-conjugated anti-chicken IgM. (e) Comparison of the staining of DT-Ab3 and DT-Ab6 cells byPE-Ab conjugate using various dilutions of the original 0.2 mg/ml stock (PE-S7 Ab;Pharamacia). (f) Affinity determination. DT-Ab6 cells (106) were incubated with 0.2 picomoles of PE-conjugated S7 Ab in various volumes to give the PE-Ab concentrations indicated; the mean fluorescence intensity (MFI) of the cells determined following washing. (g) Comparison of the IgV_H/V_L sequences of DT-Ab6 and the parental population. Selection performed using an aggregate of biotinyleted ratIgGmAbS7 with FITC streprovidin (See Example 9 for details). Sequence analysis of DT-Ab6 V_H/V_L showing 19 amino acid substitutions as compared to the perental DT40 Sequence(Seq ID Nos: 88-99). The sequences are:

FIFSTNAMG (SEQ ID NO: 88)

EWVAGIDDNGSDTRYAPAVKGRATISRDNGQSTVRLQ (SEQ ID NO: 89)

TKCAYISGYDY (SEQ ID NO: 90)

FIFSSNAMG (SEQ ID NO: 91)

EWVADIDDNGSGRRYAPAVKGRATISRDNGQSTMRLQ (SEQ ID NO: 92)

TKCTYSSDYDY (SEQ ID NO: 93)

ASVSVNPGETVKITCSGGGSYGGSYYYGWYQQKAPGSAPVSVI (SEQ ID NO: 94)

RFSGSLS (SEQ ID NO: 95)

AVYFCGNADNSGAA (SEQ ID NO: 96)

ASVSAKPGETVKITCSGGGRYIGRYYYGWYQQKTPGSAPVSMI (SEQ ID NO: 97)

RFSTSLS (SEQ ID NO: 98)

AVYVCGNVDNNGAA (SEQ ID NO: 99).--

8. On page 13, please replace the description of Figure 24 with the following:

--Figure 24. A dynasty of Protein A-specific IgMs fromDT40. (a) Selection of DT40 variants binding to derivatised magnetic beads showing the number of cells recovered following incubation ofl Os cells with 106 beads.DT-P1 and P2 were selected on streptavidin-beads coated with biotinylated-Protein A whereas DT-P3 was selected from DT-P2 on tosylated-magnetic beads directly coated with Protein A. (b) Comparison of staining of subclones of various DT-P cells by an aggregate of biotinylated Protein A with FITC-streptavidin, by Protein A that had been directly conjugated with FITC and by FITC-anti-IgM. (c) Binding of IgM in the supernatant of parental DT40 and DT-P14 bulk population to Protein A-coated plates monitored by ELISA using a mouse IgM mAb specific for chicken IgM (Southern Biotechnology) for detection. Total IgM titres were also compared as a control. (d) IgM from the supernatant of DT-P4,-P6 and P7 clones (but not from parental DT40) can be purified on Protein A, using Western blot to detect chicken IgM retained on the Protein A-Sepharose. (e)Binding of [3sS] Protein A to DTP cells. Parental DT40 (DT) or DT-P cells($5x10^5$ cells in 0. 1 ml)) were incubated on ice for lh with[$_{35}$S] Protein A (48,000 bindable cpm; 200-2000 Ci/mmol); bound cpm were determined following a single PBS wash.(f) Affinity determination. DT-P14 cells (106) were incubated with 0.7 picomoles [$_{35}$S] Protein A($7x10^{10}$ bindablecpm/mole) in various volumes to yield the Protein A concentrations indicated; bound cpm were determined following washing. (g) Staining of DT-P4 and DT-P14 cells with FITCProtein A is enhanced by performing the staining in the presence (P4+, P14+) oflmg/ml unlabelled rabbit IgG. (h) IgV gene sequences from DT-P subclones. Selection performed with strephavidim beeds coated with biotinyleted ProtA. (DT-P2 Fig. 24; See Example 9 for details). Sequence analysis of DT-P14 showing 17 amino acid substitutions as composed to the parental DT40 Sequence (Figure 24h). The sequences (SEQ ID Nos: 100-127) are:

PGGALSLV (SEQ ID NO: 100)

STNAMGWVRQAPDK (SEQ ID NO: 101)

DNGSDTRYAPAVKGRATISRDNGQSTVRLQ (SEQ ID NO: 102)

AYISGYDY (SEQ ID NO: 103

PGGPLRLV (SEQ ID NO: 104)

STNAMGWVRQAPDK (SEQ ID NO: 105)

DDGSDTRYAPAVKGRATISRDNGQRTVRLQ (SEQ ID NO: 106)

AYISGCDY (SEQ ID NO: 107)

PGGPLRLV (SEQ ID NO: 108)

STNAMGWVRQAPDK (SEQ ID NO: 109)

DDGSDTRYAPAVKGRATISRDNGQRTVSLQ (SEQ ID NO: 110)

AYISGCDY (SEQ ID NO: 111)

PGGPLRLV (SEQ ID NO: 112)

SSNAMGWVRQAPGK (SEQ ID NO: 113)

DDGSGTRYAPAVKGRATISRDNGQRTVSLQ (SEQ ID NO: 114)

AYISGCDY (SEQ ID NO: 115)

PGGPLRLV (SEQ ID NO: 116)

SSNAMGWVRQAPGK (SEQ ID NO: 117)

DDGSGTRYAPAVKGRVTISRDNGQRTVSLQ (SEQ ID NO: 118)

AYISGCDY (SEQ ID NO: 119)

ASVSVNPGETVKITCSGGGSYGGSYYYGWYQQKAPGSAPVSVI (SEQ ID NO: 120)

DDEAVYFCGNADNSGAAFGA (SEQ ID NO: 121)

ASVSVNPGETVKITCSGGGRYGGSYYYGWYQQKAPGSAPVSVI (SEQ ID NO: 122)

DDEAVYFCGNADNSGAAFGA (SEQ ID NO: 123)

ASVSANPGETVKITCSGGGRYGASYYYVWYQQKAPGSAPVSVI (SEQ ID NO: 124)

DDEAVYFCGNADNSGAAFGA (SEQ ID NO: 125)

ASVSANPGETVKITCSGGGRYGASYYYVWYQQKAPGSAPVTVI (SEQ ID NO: 126)

DDEAVYFCGNADNSGAAFGA (SEQ ID NO: 127).--

9. On page 14, please replace the description of Figure 26 with the following:

--Figure 26. Analysis of naturally-occurring constitutively hypermutating BL cell lines. The sequence of Figure 26 C is SEQ ID NO: 87; SEQ ID NO: 130.--

10. Please replace the paragraph on page 23, lines 10-31 with the following paragraph:

--In order to screen for a cell that undergoes hypermutation *in vitro*, the extent of diversity that accumulates in several human Burkitt lymphomas during clonal expansion is assessed. The Burkitt lines BL2, BL41 and BL70 are kindly provided by G. Lenoir (IARC, Lyon, France) and Ramos (Klein *et al.*, 1975, *Intervirology 5*: 319-334) is provided by D. Fearon (Cambridge, UK). Their rearranged V_H genes are PCR amplified from genomic DNA using multiple V_H family primers together with a J_H consensus oligonucleotide. Amplification of rearranged V_H segments is accomplished using Pfu polymerase together with one of 14 primers designed for each of the major human V_H families (Tomlinson, 1997, V Base database of human antibody genes. Medical Research Council, Centre for Protein Engineering, UK. ~~http://www.mrc-cpe.cam.ac.uk/~~) and a consensus J_H back primer which anneals to all six human J_H segments (JOL48, 5'-GCGGTACCTGAGGAGACGGTGACC-3' (SEQ ID NO: 1), gift of C. Jolly). Amplification of the Ramos V_H from genomic DNA is performed with oligonucleotides RVHFOR (5'-CCCCAAGCTTCCCAGGTGCAGCTACAGCAG (SEQ ID NO: 2), and JOL48. Amplification of the expressed V_H-Cμ cDNA is performed using RVHFOR and Cμ 2BACK (5'-CCCCGGTACCAGATGAGCTTGGACTTGCGG (SEQ ID NO: 3)). The genomic Cμ C1/2 region is amplified using Cμ 2BACK with Cμ 1FOR (5'-CCCCAAGCTTCGGGAGTGCATCCGCCCCAACCCTT (SEQ ID NO: 4)); the

functional Cμ allele of Ramos contains a C at nucleotide 8 of Cμ 2 as opposed to T on the non-functional allele. Rearranged Vλ's are amplified using 5'-CCCCAAGCTTCCCAGTCTGCCCTGACTCAG (SEQ ID NO: 5) and 5'-CCCCTCTAGACCACCTAGGACGGTC-AGCTT (SEQ ID NO: 6). PCR products are purified using QIAquick (Qiagen) spin columns and sequenced using an ABI377 sequencer following cloning into M13. Mutations are computed using the GAP4 alignment program (Bonfield *et al.*, 1995, *NAR 23*: 4992-99).--

11. On page 40, please replace the paragraph on lines 19-27 with the following replacement paragraph:

For the *tk-neo* insert in *tk-neo*::Cκmice, the amplified region extends from residues 607 to 1417 [as numbered in plasmid pMCNeo (GenBank accession U43611)], and the nucleotide sequence determined from position 629 to 1329. The mutation frequency of endogenous VJκ rearrangements in *tk-neo* ::Cκ mice is determined using a strategy similar to that described in Meyer *et al.*, 1996. Endogenous VJκ5 rearrangements are amplified using a Vκ FR3 consensus forward primer (GGACTGCAGTCAGGTTCAGTGGCAGTGGG (SEQ ID NO: 7)) and an oligonucleotide LκFOR (Gonzalez-Fernandez and Milstein, 1993, ~~PNAS~~ *Proc. Natl. Acad. Sci. USA 90*: 9862-9866) that primes back from downstream of the Jκ cluster.

11. On page 43, please replace the paragraph on lines 19-32 continuing to page 44, lines 1-3, with the following replacement paragraph:

Genomic DNA is PCR amplified from 5000 cell equivalents using Pfu Turbo (Stratagene) polymerase and hotstart touchdown PCR [8 cycles at 95°C 1'; 68-60°C (at 1°C per cycle) 1 min.; 72 °C 1 min., 30 sec.; 22 cycles @ 94°C, 30 sec."; 60 °C, 1 min.; 72°C, 1 min., 30 sec.]. The rearranged Vλ is amplified using CVLF6 (5'-CAGGAGCTCGCGGGGCCGTCACTGATTGCCG (SEQ ID NO:8); priming in the leader-Vλ intron) and CVLR3 (5'-GCGCAAGCTTCCCCAGCCTGCCGCCAAGTCCAAG (SEQ ID NO:9); priming back

from 3' of Jλ); the unrearranged Vλ1 using CVLF6 with CVLURR1 (5'-GGAATTCTCAGTGGGAGCAGGAGCAG (SEQ ID NO:10)); the rearranged V_H gene using CVH1F1 (5'-CGGGAGCTCCGTCAGCGCTCTCTGTCC (SEQ ID NO:11)) with CJH1R1 (5'-GGGGTACCCGGAGGAGACGATGACTTCGG (SEQ ID NO:12)) and the C_λ region using CJCIR1F (5'-GCAGTTCAAGAATTCCTCGCTGG (SEQ ID NO:13); priming from within the J_λ-C_λ intron) with CCMUCLAR (5'-GGAGCCATCGATCACCCAATCCAC (SEQ ID NO:14); priming back from within C_λ). After purification on QIAquick spin columns (Qiagen), PCR products are cut with the appropriate restriction enzymes, cloned into pBluescriptSK and sequenced using the T3 or T7 primers and an ABI377 sequencer (Applied Biosystems). Sequence alignment (Bonfield *et al.*, 1995, *supra*) with GAP4 allowed identification of changes from the consensus sequence of each clone.